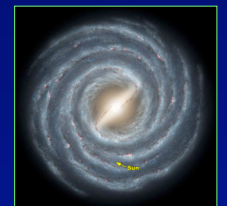
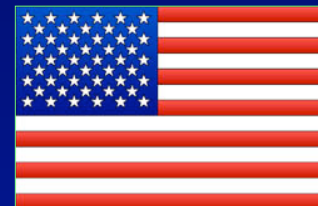


Functional MRI Analysis

Robert W Cox

robertcox@mail.nih.gov



PDF of this presentation is at

<http://goo.gl/KTf6y>

I have absolutely no relevant or revelatory financial or pecuniary interest or relationship to disclose or reveal with regard to or in the vicinity of the subject matter or content of this presentation or didaction.

(Damn)

ISMRM - May 2011

To Dream the Impossible Dream

- *i.e.*, To explain fMRI Analysis in 25 min
- Basis for fMRI time series analysis:
 - 10-20 inter-twined concepts
 - pre-processing ; individual subject analysis ; group analysis ; connectivity ; ...
- Many seem simple, but ***each*** one has subtleties and points of contention
- ☀ Can only cover the most central ideas now
⇒ **Absolute Beginners**: Confusion Ahead!

Some Goals of fMRI Analyses

- **Task-based experiments**
 - Per subject: estimate amplitude of BOLD response to each different type of stimulus
 - Find+model inter-regional correlations between fluctuations in BOLD responses

- **Resting-state experiments**
 - Measure spatial patterns in coherent fluctuations in spontaneous BOLD

- **Group level**
 - Combine and contrast per subject results

Conceptual Basis - 1

- **Time shifting** = pretend get 3D snapshot
- **Despiking** = remove large blips
- **Image Registration** (AKA alignment)
 - intra-EPI time series, and EPI ↔ Structural
- **Blurring in space** = lower resolution :-(& less noise :-) & more group overlap :-)
- **Masking** = ignore non-brain voxels
- **Scaling** = normalizing data amplitude
 - Makes inter-subject comparisons more valid

Conceptual Basis - 2

★ Time series regression

- model of the BOLD response in the data = Hemodynamic Response Function ⊗ stimulus timing
- plus baseline (null hypothesis) model
- plus physiological noise
- plus allowing for serial correlation

★ Talairach-ing = Spatial Normalization

- Talairach, MNI-152, ...
- affine and nonlinear spatial transformations

Conceptual Basis - 3

- ✪ **Group Analyses** = Putting it all together
 - ANOVA, LME, Meta-Analyses, ...
- ✪ **Blobs** = Spatial models of activation
 - Assigning statistical significance to blobs
- ✪ **Connectivity** = Inter-regional analyses
 - SEM, PPI, SVAR, DCM, ...
 - Resting state fMRI (Connectome!)
- **Dimensional factorization**
 - Components, such as PCA, ICA, ...

Conceptual Basis - 4

- **Data Formats** = NIfTI-1.x is your friend
- **Software** for fMRI analyses: *open-source
 - AFNI^{*}, BrainVoyager, FSL^{*}, SPM^{*}, ...
 - Whichever you use, **don't blindly assume** the software works perfectly all the time
- Most important thing I will say today
Understand and check the steps applied to your data!
- 2nd most important: **Is no "best" way to analyze data, just "reasonable" ways**

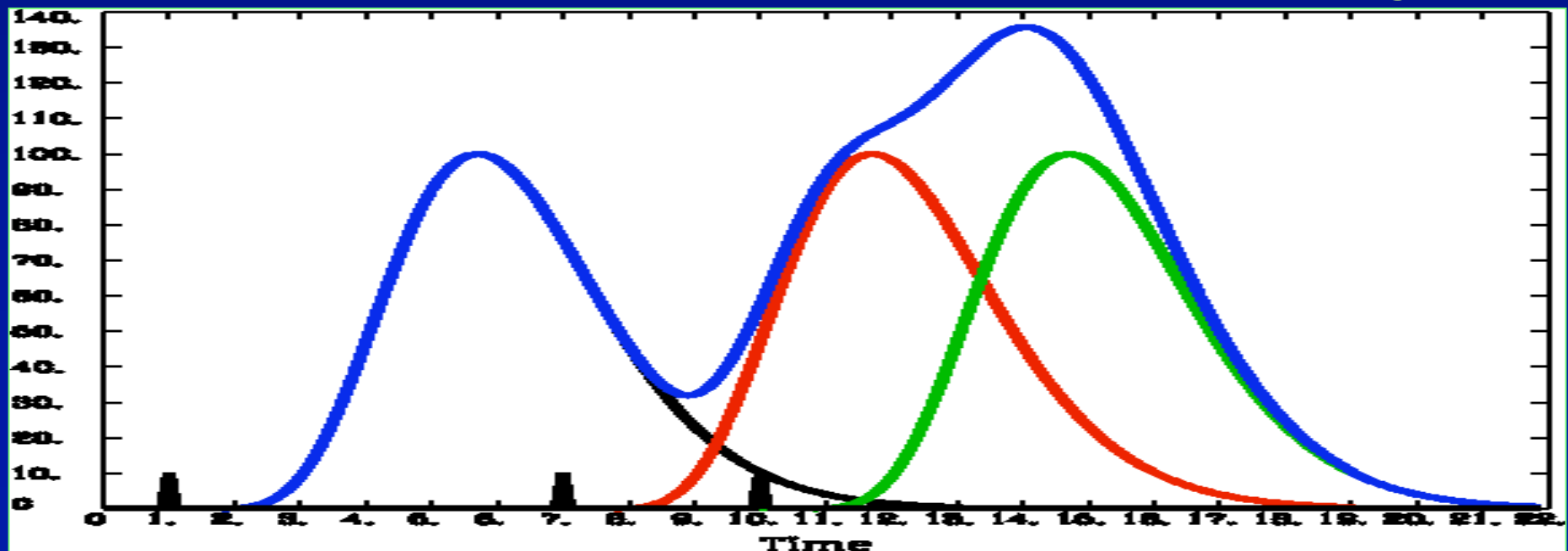
★ Time Series Regression

- After pre-processing the images:
 - Each voxel time series is (separately) fit to an idealized model of the BOLD effect
 - Plus other (nuisance) components
 - Baseline drift, physiological artifacts, ...

- Estimated parameters of the BOLD model are the "**activation map**"
 - Amplitude of response = most common
 - Shape of response can also be modeled
 - Statistics on parameters allow thresholding

Basic BOLD Model

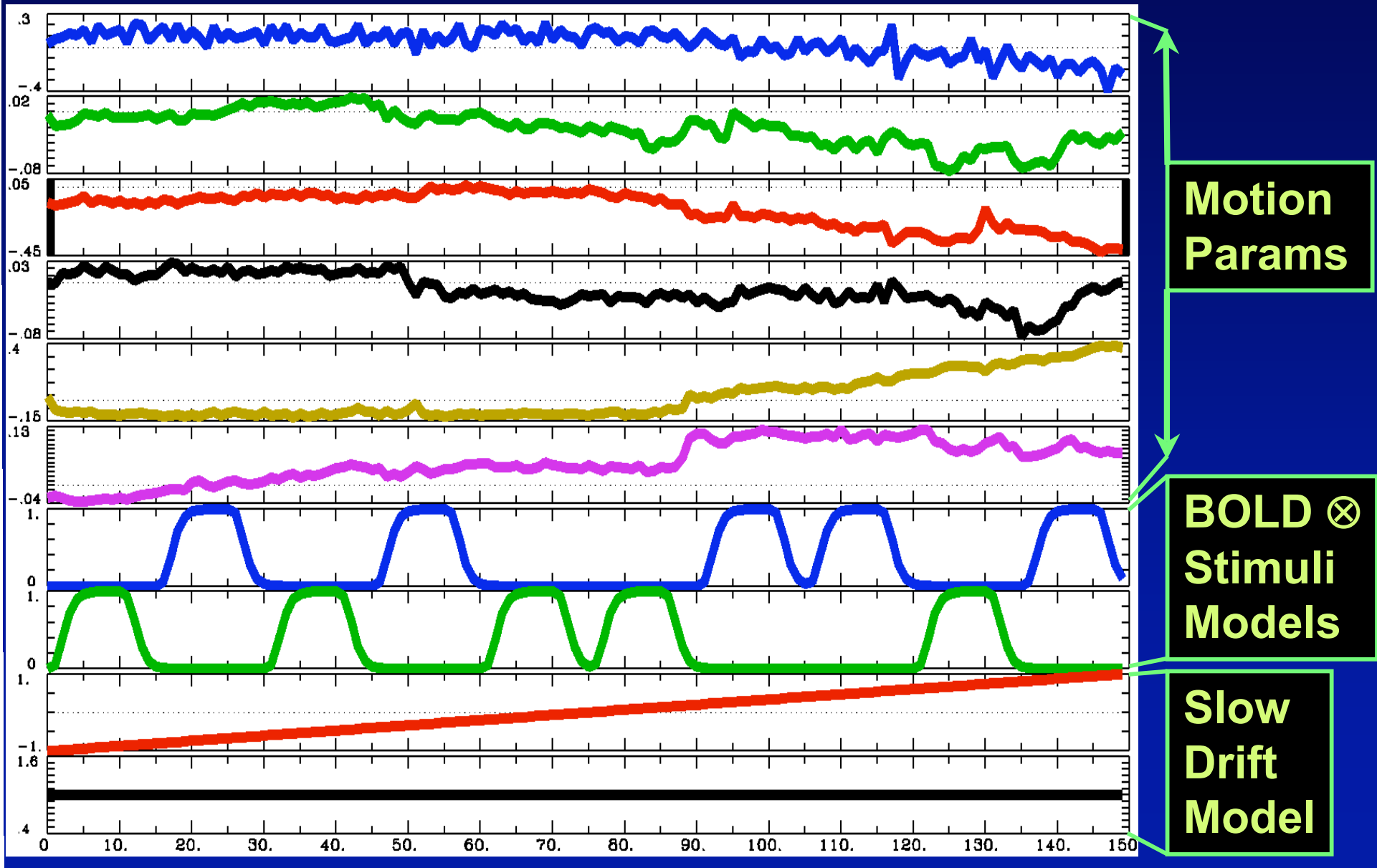
- Assumptions:
 - BOLD response starts ≈ 2 s after "activity"
 - Rises to peak about ≈ 4 s later
 - Drops to baseline about ≈ 5 s post-activity
 - Overlapping (in time) BOLD responses from separate events add up = **linearity**



Further Model Pieces-Parts

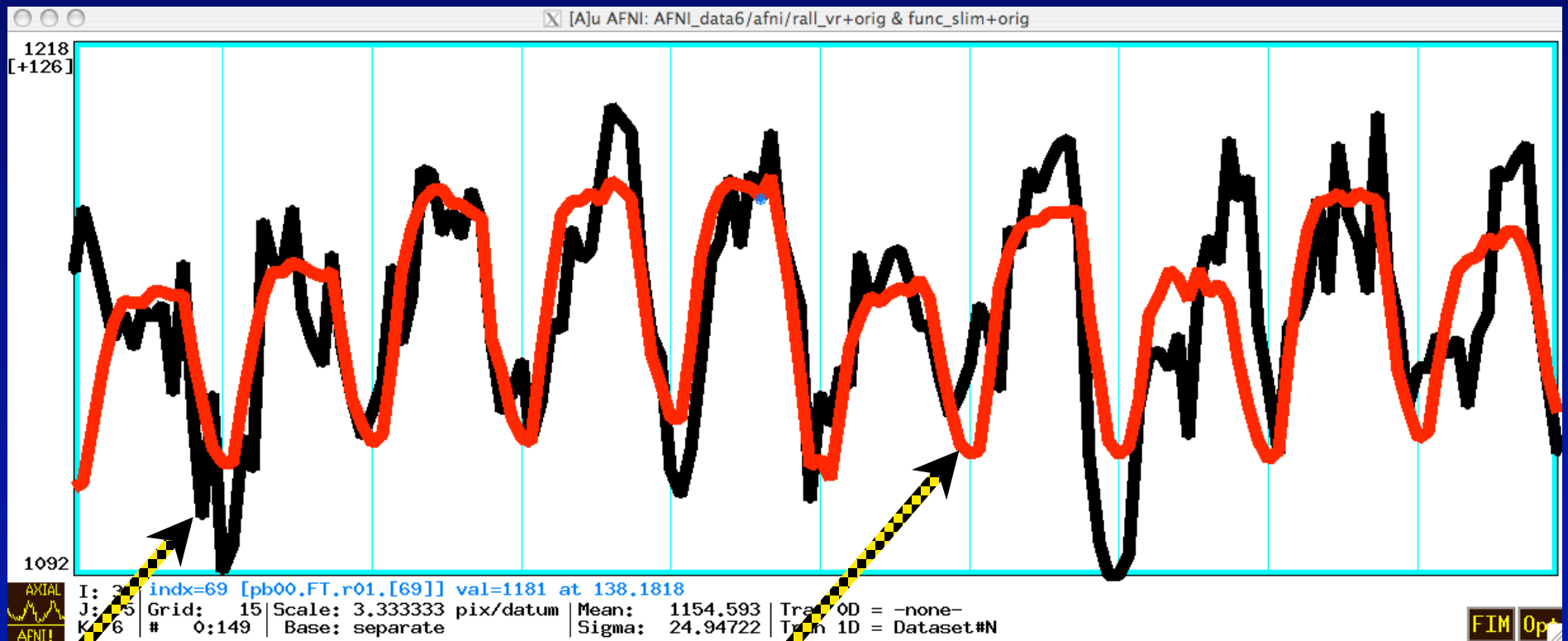
- FMRI data = pretty noisy \Rightarrow
 - Need multiple copies of each stimulus type
 - Assume BOLD responses same within type
- Slow drifting terms in baseline *highpass filter*
- Residual effects of subject movements
 - Use motion parameters as extra regressors
- Include physiological regressors (**RetroICOR**)
 - From monitoring heartbeat & respiration
- Serial correlation in noise \Rightarrow use **GLSQ**

Sample Linear Regression Model



One Voxel's Time Series

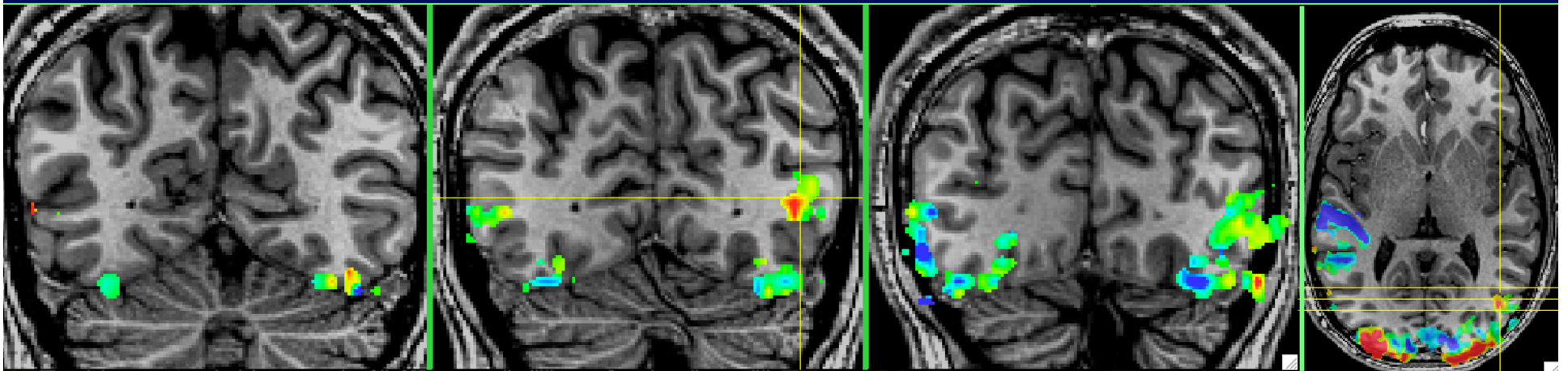
- This is good data at a high signal voxel
- 2 stimulus classes; 1 block every 30s; TR=2s



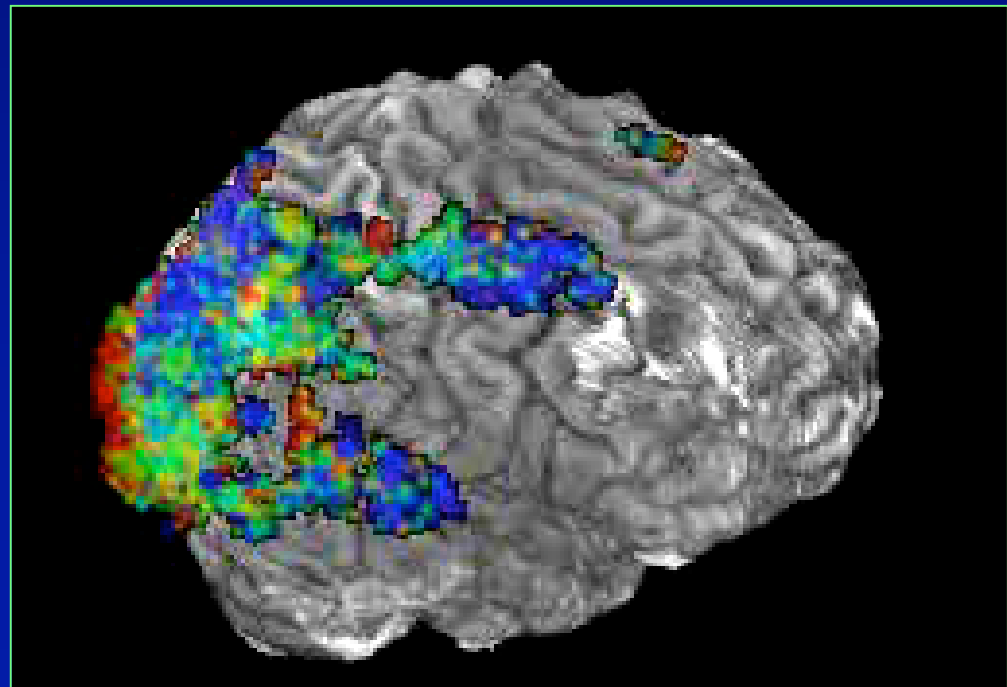
Black = 150 data points **Red** = fitted model (BOLD++)

Data: Mike Beauchamp/UTexas

Results from One Subject



ShowThru
rendering of
difference
between visual
and auditory
BOLD
amplitudes

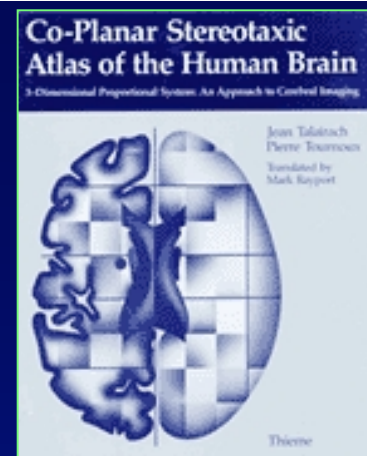


★ Talairach-ing

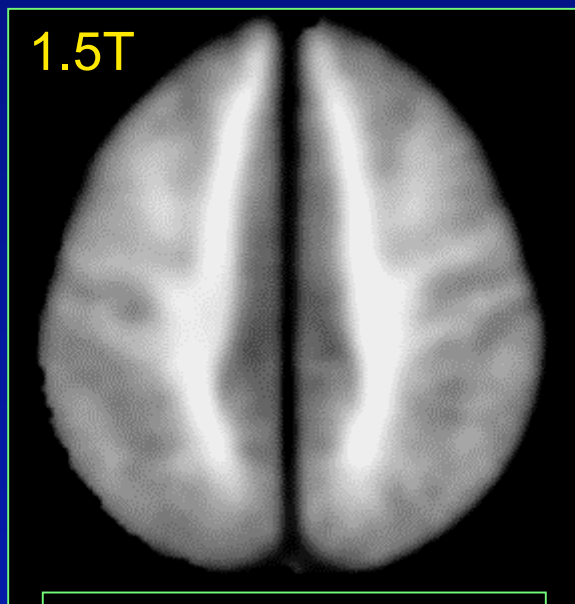
- For combining and contrasting results across groups of subjects
- Align 3D brain images (usually structural volumes) to a common template
 - Assumption: function follows structure
- Then merge results on a voxel-wise basis on this new grid
 - Accuracy of alignment = 5-10 mm
 - Spatial blurring = more inter-subject overlap

Templates

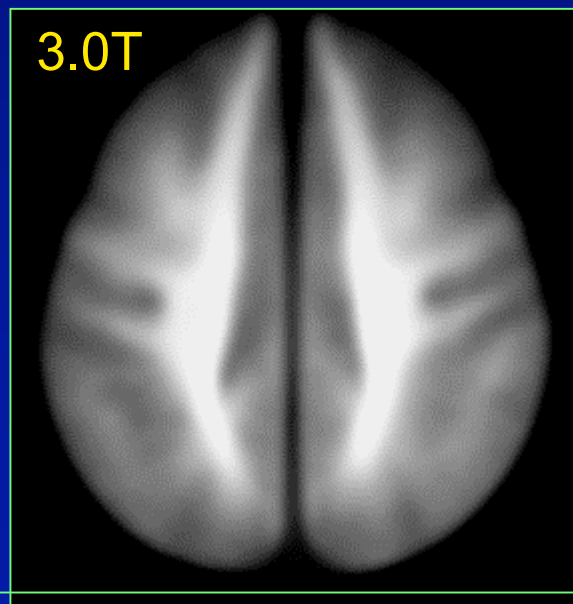
- Ye Good Olde Days = Talairach-Tournoux atlas



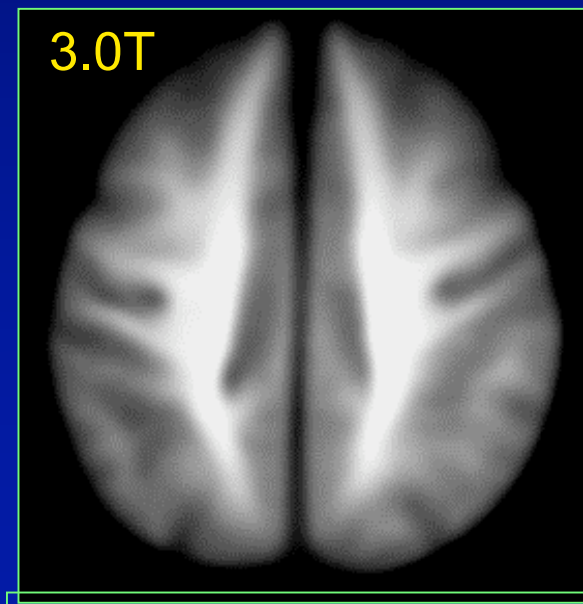
- Decadent modern times = MNI-152 template = average of 152 brain images



MNI-152 (affine)



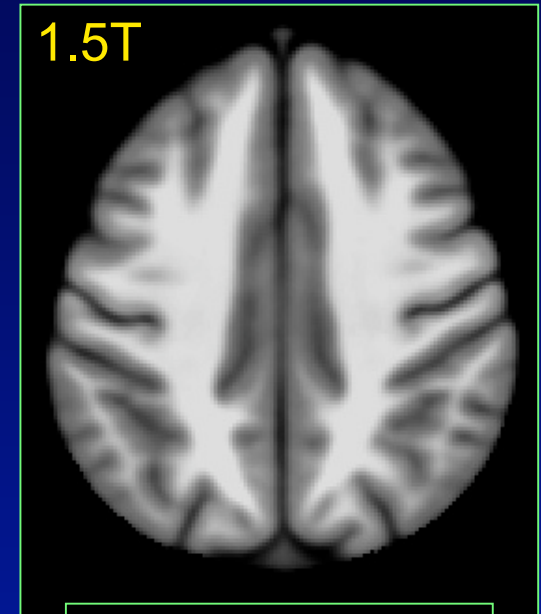
FCON-1000 (affine)



FCON-1000 (poly9)

Custom Templates

- Can register all subjects in study together iteratively
 - Then average to get a study-specific template
 - Can use high order nonlinear spatial warps for better structural feature alignment



285 subjects
(DARTEL-SPM)

Data: Shane Kippenham/NIH

- Alternatives:
 - ROI or Atlas-based analyses [cf. **Collins**]
 - Cortical surface-based analyses [cf. **Greve**]

★ Group Analysis

- Group analysis is done in 2 stages:
 - Individual subject analyses reduce EPI time series to BOLD response parameters
 - Inter-subject analysis is done on these parameters (e.g., measures of amplitude)
 - Usually have some estimate of reliability of these parameters (e.g., standard deviation)
- Normalization of data magnitude and spatial normalization are important steps

Flavors of Group Analysis - 1

- t -tests for simple 2-way contrasts
- ANOVA of various complexities for more intricate collective effects
 - Usually end up wanting to do t -tests on these "main" effects to see **What's Up** (*Doc*)
 - Plain ANOVA relies on many assumptions about distribution of randomness
 - Independent noise (or all samples are correlated the same way; "sphericity") ; Gaussianity ; Homoscedasticity (all samples have same variance) ; Balanced designs

Flavors of Group Analysis - 2

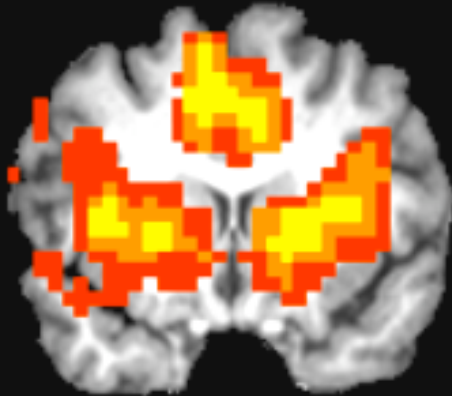
- Linear Mixed Effects (LME) models can generalize **ANOVA** to allow for variations from such assumptions

- Meta-Analysis: Statistics run on statistics
 - Which is exactly what we are doing in FMRI
 - Many developments in the 1990s
 - Can be applied to FMRI data, using not just the individual subject amplitudes, but also their reliability estimates; cf. **AFNI** and **FSL**
 - Can also model non-Gaussianity (outliers)

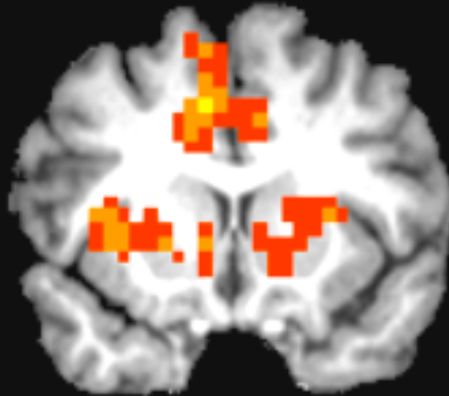
Meta-Analysis Results

Meta-Analysis

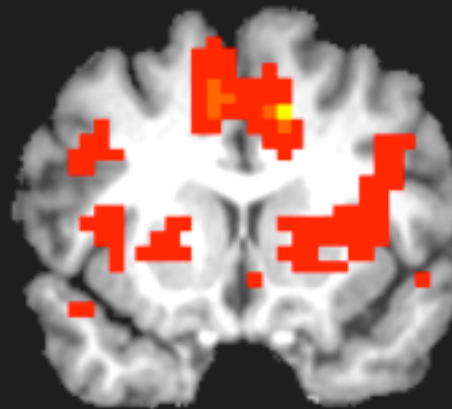
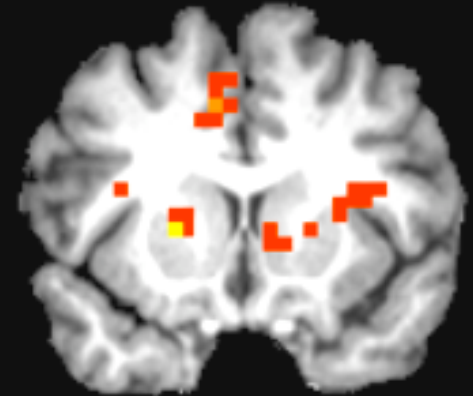
Task A: 20 sub



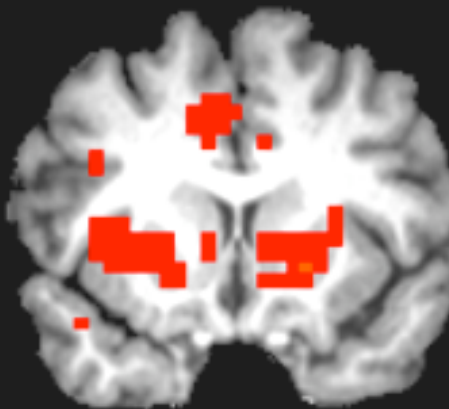
Task B: 12 sub



Task C: 11 sub



ANOVA



Yellow = Stronger



Data: James Bjork/NIH

★ Blobs! [AKA Clusters]

- For most purposes, if we saw that all the statistically significant activation was just in tiny and scattered clusters, we would be suspicious and upset
- We not only threshold on voxel-wise t - or F -statistics, but we also threshold on size of contiguous supra-threshold clusters
- Allows us to lower the per-voxel threshold by raising the cluster-size threshold to maintain error rate control

Blob Significance

- Probability that a smooth *noise-only* image would produce a blob, with each voxel above a given threshold and the size of the blob above a given cutoff
- Cannot be calculated in closed form :-(

- Two approaches available:
 - Asymptotic formula for high per-voxel thresholds and high degrees of smoothness K Worsley
 - Direct Monte-Carlo simulation (brute force)
 - Which to use? Depends on your software!

★ Connectivity

- **FMRI basis:** Fluctuations in neural activity \Rightarrow fluctuations in BOLD signal
- \therefore Task performance changes between repetitions can give coherent signal changes in remote brain regions
- Can look for *causal* changes also:
 - e.g., Predictability of one region's data from another's data at a *previous* time step
 - Limited TR of FMRI data makes this iffy
 - Probably need $TR \leq 1s$ to do this well

Connectivity - Jargon

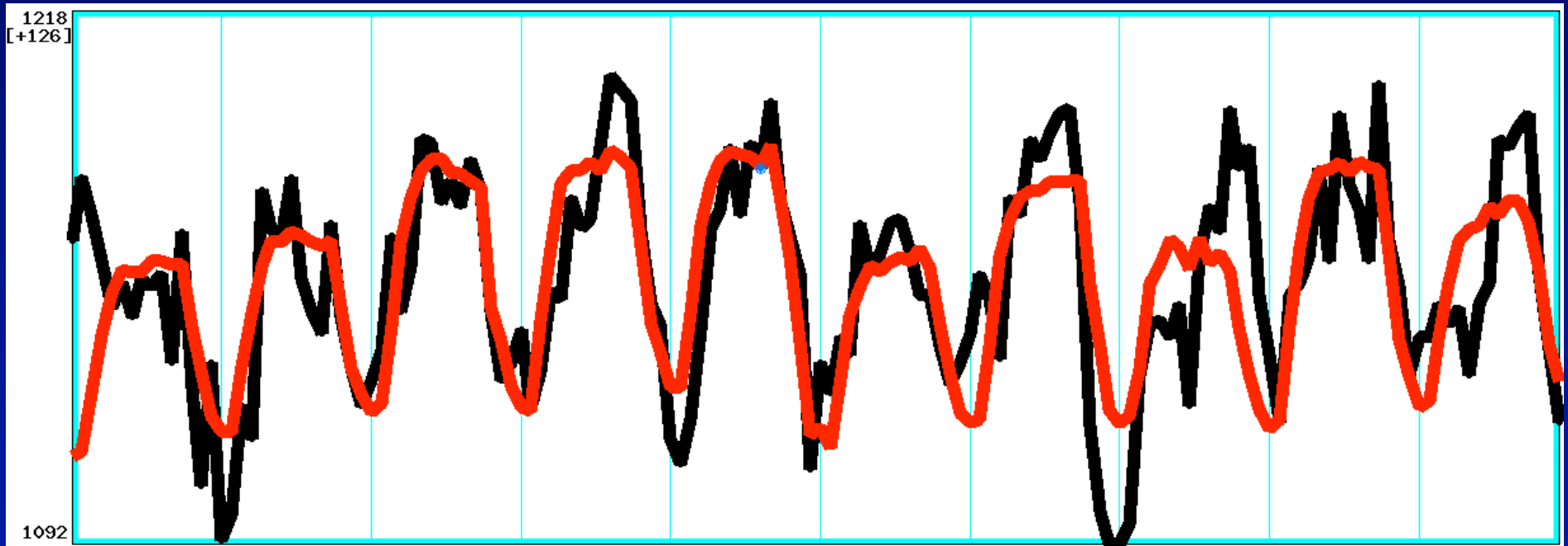
- **Functional** connectivity
 - Means the regions are connected in some sense of doing the same function
 - Could be a common driver (e.g., thalamus) with no direct connections

- **Effective** connectivity
 - Means that changes in one region have an effect on other regions (a stronger statement)

- **Causal** connectivity
 - Similar; usually implies temporal ordering

Task-Based Connectivity

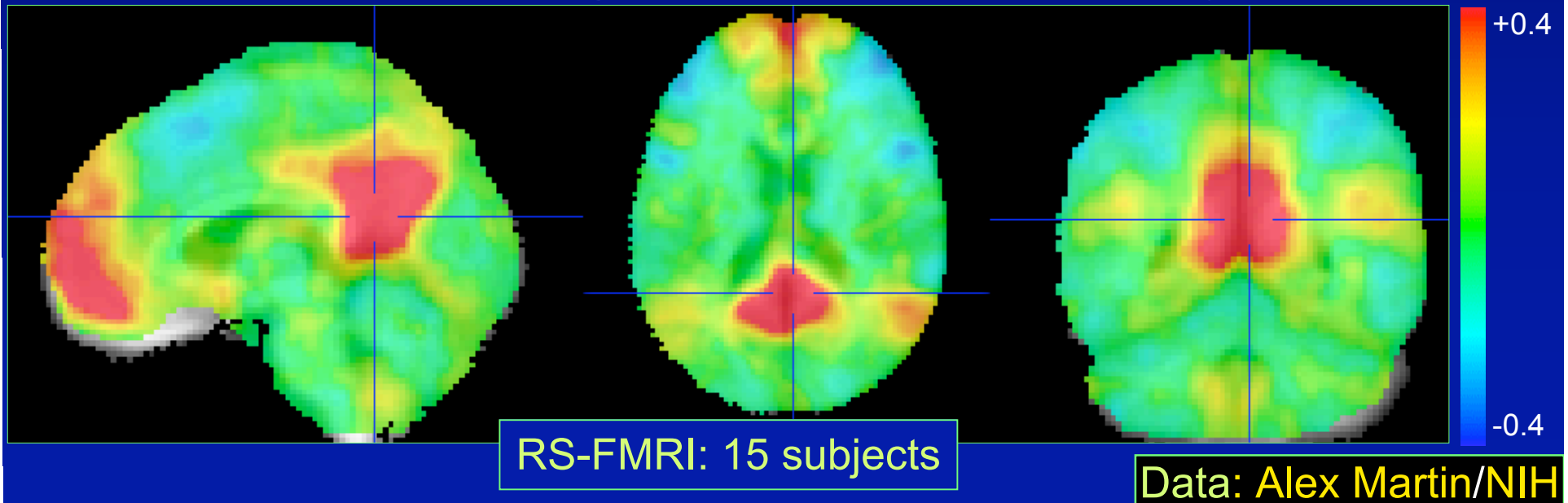
- Fluctuations from model fit can be bigger than noise; recall this graph from 1 voxel



- So can subtract the fit and then look for inter-voxel correlations (if have enough data)

Flavors of Connectivity - 1

- Simple correlation from a seed region (or voxel) with all other voxels in brain
 - Ambitiously: Correlate All-with-All :-)
- Then group analysis for statistical power
- Used in resting-state FMRI analyses



Flavors of Connectivity - 2

- PPI = **P**sycho-**P**hysiological **I**nteraction
 - I call it "Context Dependent Correlation"
 - Augment the regression model with data time series averaged from a seed region
 - And multiplied by **+1** in context **A**, **-1** in context **B**, and **0** in other cases (e.g., baseline)
 - Fit parameter for new regressor measures fluctuations in EPI signal whose correlation with seed region **changes** between contexts (**A & B**)
 - Context = "Psycho" ; EPI/BOLD = "Physio"

Flavors of Connectivity - 3

- Network models use multiple regions, try to fit multiple dependencies amongst them
 - FMRI noise means must average over pre-chosen regions before network hunting+fitting
 - Anatomical ROIs or Functional ROIs?
- Instantaneous directional effects:
 - Structural Equation Modeling (**SEM**)
- Delayed (causal) effects:
 - Dynamic Causal Modeling (**DCM**)
 - Structural Vector AutoRegression (**SVAR**)

Connectivity Conclusions

- Often: make statement about *changes* in connectivity between two situations
 - Absolute connectivity statements are somewhat less common (though not rare)
- When contrasting subject groups, must be careful that physiological differences (e.g., respiration) are accounted for
 - Especially in resting-state studies, which don't have any task-timing to which we can tie down the analysis

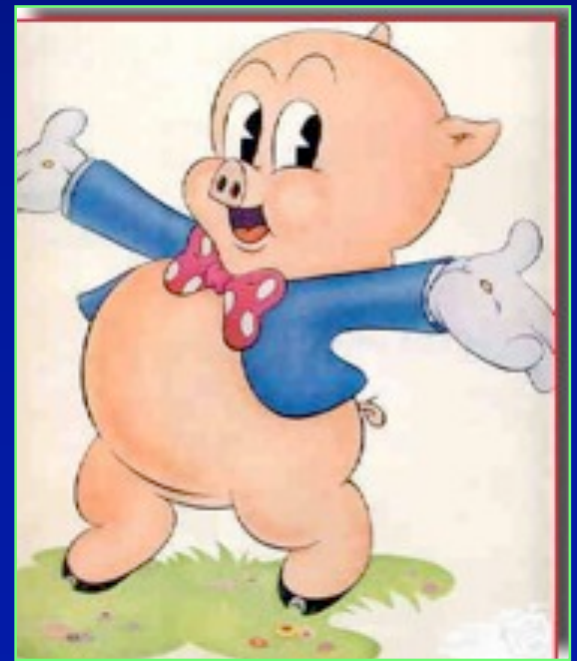
Final Gratuitous Remarks

- Multi-stimulus linear regression models for task-based fMRI appear in mid-1990s
- Since then, most task-based fMRI time series analysis improvements have been incremental **and/or** controversial **and/or** of limited scope — **IMHO**
- Are we near the limit of what kind of information can be gleaned from current-technology fMRI datasets?
 - **Or do we just need to be cleverer?**

Th'Th'That's All Folks!

- Thanks must go to
 - Ziad Saad, Gang Chen, Rick Reynolds, Daniel Glen
 - James Hyde, Peter Bandettini, Andrzej Jesmanowicz
 - Elliot Stein, Jeff Binder, Steve Rao, Alex Martin, Leslie Ungerleider, Ted Deyoe, and too many more brain-ologists to name herein

<http://goo.gl/KTf6y>



Data: Warner Bros.